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Monoclonal Antibody (mAb)-Based Biotherapy Options for B-lineage Non-Hodgkin's Lymphoma (NHL)

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In recent years new biotherapy options have emerged for patients with B-lineage Non-Hodgkin's Lymphoma (NHL). A series of novel mAbs with specificity for a variety of surface antigens are currently under evaluation. These include anti-CD20 mAb (ofatumumab, veltuzumab, ocrelizumab, ocaratuzumab, obinutuzumab, ublituximab), anti-CD19 mAb (MOR208), anti-CD22 mAbs (epratuzumab, inotuzumab ozogamicin) and anti-CD16/CD30 mAb (TandAb® AFM13) [1-12].

Targeting CD20

Rituximab (RTX, Rituxan, Roche/Biogen Idec) is the best known anti-CD20 mAb and has been used both for biotherapy of patients with B-lineage NHL who experience a recurrence of their disease after frontline therapy as well as for frontline treatment of B-lineage NHL patients who are at high risk to experience a recurrence after chemotherapy. Combination of RTX with chemotherapy (e.g. RTX + CHOP) has improved treatment outcomes and is now considered the standard of care for many forms of NHL, including diffuse large B-cell lymphoma (DLBCL) [1]. However, resistance to RTX does occur and compromises the outcome of B-lineage NHL patients receiving RTX as part of their treatment plan [2]. Bioengineering has been applied to generate new anti-CD20 mAb to overcome RTX resistance [3-8]. Ofatumumab (OFA, Genmab AC and GlaxoSmithKline) is a human mAb that targets unique epitopes of the CD20 antigen [4]. OFA is used for biotherapy of patients with well-differentiated small lymphocytic lymphoma/chronic lymphocytic leukemia (CLL) who do not respond to fludarabine and alemtuzumab (Campath 1-H). Veltuzumab (Immunomedics, Inc.) is a humanized, type I (i.e., RTX-like as opposed to tositumomab-like) anti-CD20 IgG1 mAb, with higher affinity to CD20 and improved complement-dependent cytotoxicity (CDC) against B-lineage NHL cells. This mAb is also being evaluated in combination with the humanized anti-CD74 antibody milatuzumab [9]. Ocrelizumab (Roche/Biogen Idec) is also a type I humanized mAb that has enhanced potency against B-lineage NHL cells as well as improved ability to cause antibody-dependent cell-mediated cytotoxicity (ADCC) against NHL than RTX [5]. Both antibodies are currently being evaluated in early phase clinical trials. Ocaratuzumab (Mentrik Biotech, LLC) is a type I humanized mAb with increased affinity for CD20 as well as low affinity FcγRIIIa receptor involved in ADCC. It has shown promising early activity in a Phase I clinical study [6]. Obinutuzumab (Genmab AC) is a type II humanized anti-CD20 mAb that has shown promising preclinical as well as early clinical activity against RTX-resistant B-lineage NHL. It is now being compared to RTX in randomized clinical trials [7]. Ublituximab (TG Therapeutics, Inc) is a chimeric mAb with superior ADCC activity that showed very promising activity against RTX-resistant NHL in early clinical testing [8].

Targeting Surface Antigens Other than CD20

MOR208 (MorphoSys AG) is a new anti-CD19 mAb, which was well-tolerated and showed promising biologic activity in early clinical testing [10]. Epratuzumab (Immunomedics, Inc.) is a humanized anti-CD22 mAb that showed single agent clinical activity in NHL patients. TandAb® AFM13 (Affimed Therapeutics AG) is specifically designed to treat CD30-antigen NHL. It binds to both CD30 on malignant cells and CD16 on natural killer cells and mediates ADCC. This bispecific mAb showed a promising safety and activity profile in early clinical evaluation [11,12].

Further development of some of these new mAb against CD20 or non-CD20 target antigens may overcome RTX resistance and thereby provide the foundation for therapeutic innovations with unprecedented clinical activity against poor prognosis NHL.

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